ARIC Manuscript Proposal # 1316

PC Reviewed: _11/_13_/07	**Status: __A__**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiac autonomic dysfunction and the risk of Parkinson's disease in the Atherosclerosis Risk In Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Cardiac autonomic dysfunction and PD

2. Writing Group:

Writing group members: Alvaro Alonso, Xuemei Huang, Thomas H. Mosley, Honglei Chen, Sunil K. Agarwal

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AA_ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data analysis: 3 months
First draft: 3-6 months

4. Rationale:

Parkinson's disease (PD) is a disorder characterized pathologically by loss of dopaminergic neurons in the substantia nigra of basal ganglia. Its main clinical manifestations are resting tremor, rigidity, bradykinesia and postural instability. In addition to this classical motor symptoms, autonomic dysfunction (orthostatic hypotension and other vasomotor abnormalities, sialorrhea, hyperhidrosis, erectile dysfunction, constipation, etc), have been well described in PD patients,[1] and they may predate the diagnosis of PD.

There are two studies that have reported the association of symptoms of autonomic dysfunction (decrease in bowel movements, erectile dysfunction) and an increased risk of developing PD.[2, 3] Both studies, however, used self-reported information to define the exposure. Also, the study populations included only men (of Asian ancestry in the first, whites in the second). There are no prospective studies showing an association between objective measurements of autonomic dysfunction and the future risk of PD. In addition, this association has not been studied in women or in blacks.

Cardiac autonomic dysfunction, defined as lower heart rate variability, is more frequent among PD patients than among controls.[4-6] The mechanism might be related to the degeneration or dysfunction of sympathetic and parasympathetic neurons (as attested by the presence of Lewy body inclusions in these cellular types.)[7] No studies, though, have assessed whether this dysfunction occurs before the diagnosis of PD, which is classically based on motor symptoms. Finding an association between cardiac autonomic dysfunction and the risk of PD could provide new clues in our understanding of the ethiopathogenic process leading to PD and an objective measurement for the early detection of PD cases.

5. Main Hypothesis/Study Questions:

Our objective is to estimate the association of cardiac autonomic dysfunction, assessed through heart rate variability, and the occurrence of PD. As a secondary objective, we will evaluate and compare the time course of heart rate variability in PD patients and individuals without PD. We hypothesize that individuals with cardiac autonomic dysfunction, identified as lower heart rate variability, have higher probability of presenting clinical PD. Also, PD patients have a worsening in their autonomic dysfunction over time.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

We will estimate prospectively the association between heart rate variability at baseline and the subsequent risk of PD in ARIC study participants. Incidence of PD will be compared among different groups defined according to their cardiac autonomic function.

Exclusion criteria

- Participants who did not consent to participate in non-CVD research
- Participants without information on heart rate variability at baseline

Exposure assessment

Cardiac autonomic dysfunction will be estimated from heart rate variability measures collected at baseline (visit 1), as described in previous ARIC publications.[8, 9] Specifically, we will use:

- Mean normal-to-normal R-R interval length
- Standard deviation of normal-to-normal R-R intervals
- Root mean square of successive differences in normal-to-normal R-R intervals

- High frequency and low frequency spectral components, and low to high frequency ratio

All exposures will be categorized in quartiles. In addition, to explore the change in heart rate variability over time in PD patients, we will use heart rate variability information collected in visit 3 (year 9 of follow-up). The information will be used in a similar fashion to the baseline data (correcting heart rate variability measures obtained in visit 3 to allow comparison with visit 1, as suggested in Schroeder et al, ref 9)

Outcome ascertainment

Potential PD cases have been identified from multiple sources: hospital discharge records, medication data from follow-up surveys, death certificates, as well as self-reports at visit 4 (1996-1998) when participants were asked 'Have you ever been told by an MD that you have PD?' So far, 172 cases have been identified, and 111 have been confirmed by Dr. Xuemei Huang. Though we do not have the date of onset for PD cases, we can assume that most of these are incident cases, given the age range of participants at baseline.

Statistical analysis

Association between cardiac autonomic dysfunction and PD will be estimated using logistic regression, with presence of a PD diagnosis as the outcome. We will adjust for age, sex, race, center, smoking, caffeine and alcohol consumption, and diabetes as potential confounding factors. In all analyses, we will use quartiles of the different measures of heart rate variability as main independent variable, with the lowest quartile as reference. To estimate trends, we will use heart rate variability measures as continuous variables. In a secondary analysis, we will exclude participants with diabetes at baseline (diabetes can cause autonomic neuropathy and it could be related to PD risk).

Limitations

- Misclassification of exposures: to better define the cardiac autonomic function in ARIC participants, additional tests would have been useful (e.g. tilting tests). However, the available information compares favorably with any other published paper on this issue. In addition, data from studies conducted on PD patients suggest that these same variables are enough to detect this particular type of autonomic dysfunction.[4, 5]
- Misclassification of the outcome: ascertainment of PD cases has not been obtained through direct examination from ARIC participants. Then, some cases will be lost (false negatives) and some participants reporting PD might not have the disease (false positives). In general, however, previous analyses using PD as outcome in the ARIC cohort have found expected associations: increased risk with age and in men, lower risk among smokers and coffee drinkers. An additional problem is the potential presence of prevalence cases in the cohort. Based on the available data, we cannot separate prevalent from incident cases. To partially avoid this problem, we will conduct a sensitivity analysis excluding individuals older than 60 at baseline: because PD incidence is very low before age 60, cases identified among people younger than 60 at baseline more likely will be incident cases.

- Confounding: the etiology of PD is unknown. The main known risks factors for PD are age, sex, smoking and coffee intake. Fortunately, this information is available in the ARIC study. Thus, though some unmeasured confounding is possible, analyses adjusted for the mentioned variables will reasonably control confounding. We will also adjust our analysis for other main causes of autonomic neuropathy, i.e. diabetes and alcohol intake, though it is not clear whether these conditions are associated to the risk of PD. Other causes of autonomic dysfunction are less frequent and do not affect the risk of developing PD.
- Selection bias: the ARIC study is a prospective study. Selection bias, then, can arise from differential follow-up. We do not expect that the potential association between cardiac autonomic dysfunction and PD will be different among retained participants and individuals lost to follow-up. Nonetheless, in an additional analysis we will try to correct the potential selection bias derived from censoring using inverse probability weighting.[10]

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes _ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _X_ Yes _ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __ Yes _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __ Yes __ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php
___X__ Yes _____ No No overlap with existing proposals

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

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4. Kallio M, Haapaniemi T, Turkka J, et al. Heart rate variability in patients with untreated Parkinson's disease. Eur J Neurol 2000;7:667-72.
5. Barbic F, Perego F, Canesi M, et al. Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. Hypertension 2007;49:120-6.
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8. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes 2002;51:3524-31.
9. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability. The Atherosclerosis Risk in Communities (ARIC) Study. Hypertension 2003;42:1106-11.
10. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615-25.